Dissertation on

A comparative study of oral clonidine and oral diazepam premedication for haemodynamic stability in patients undergoing craniotomy

Madras Medical College
MD Anaesthesiology

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Chennai
Tamilnadu

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Certificate

This to certify that this dissertation entitled ”**A comparative study of oral clonidine and oral diazepam premedication for haemodynamic stability in patients undergoing craniotomy**”, has been prepared by **Dr.R.Uma**, post graduate student in M.D.Anaesthesiology, Madras Medical College, Chennai, done under the guidance and supervision of **Prof. Dr.G.Sivarajan, M.D., D.A**., Dept. of Anesthesiology at Madras Medical College and Government General Hospital, Chennai in partial fulfillment of the regulations for the award of the degree of M.D. (Anaesthesiology), examination to be held in February 2005.

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Certificate

This to certify that this dissertation entitled “A comparative study of oral clonidine and oral diazepam premedication for haemodynamic stability in patients undergoing craniotomy”, has been prepared by **Dr.R.Uma,** post graduate student in M.D.Anaesthesiology done under my direct guidance and supervision at Madras Medical College, Chennai in partial fulfillment of the regulations for the award of the degree of M.D. (Anaesthesiology), examination to be held in February 2005.

She has shown keen interest in preparing this dissertation and I have a great pleasure in forwarding this dissertation to the University.

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Declaration

I hereby declare that this dissertation entitled "A comparative study of oral clonidine and oral diazepam premedication for haemodynamic stability in patients undergoing craniotomy", has been prepared by me under the guidance of **Prof.Dr.G.Sivarajan,M.D.,D.A** Professor and Head of Department of Anaesthesiology, Madras Medical College, Chennai in partial fulfillment of the regulations for the award of the degree of M.D. (Anaesthesiology), examination to be held in February 2005.

This study was conducted at Madras Medical College and Government General Hospital, Chennai.

This dissertation has not been submitted by me previously to any university for the award of any degree or diploma.

Date:
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CONTENTS

INTRODUCTION

Anaesthesia for intracranial surgery.

If good anaesthesia is to be provided to the patient undergoing surgery for an expanding intracranial lesion, certain principles should be borne in mind. These principles include:

1. Careful preoperative assessment of the patient.

2. Awareness of abnormal intracranial dynamics in the presence of an intracranial mass lesion

3. The importance of a smooth induction of anesthesia

4. Adequate depth of anesthesia and complete muscle paralysis before laryngoscopy and intubation

5. The choice of a maintenance technique that does not increase ICP and allows adequate CPP.

Failure to adhere to these principles may lead to sudden increases in intracranial pressure, decreased cerebral perfusion pressure, and regional ischemia. In the closed skull, internal herniation of brain tissue through the tentorial notch or the foramen magnum may occur. External brain herniation, with increased bleeding and rupture of cerebral cortex, may occur after the dura mater has been opened if these anesthetic parameters are not controlled. Neuroanesthesia, therefore, plays an important role in the reduction of morbidity and mortality in the surgery of intracranial lesions of all types, including neoplasm's - not only in the operating room, but also in the pre- and postoperative care of the neurosurgical patient.

AIM

The aim of the study is to evaluate the efficacy of oral clonidine as a premedicant in providing intra-operative haemodynamic stability in neurosurgical patients undergoing craniotomies.

REVIEW OF LITERATURE

Cerebral circulation

The brain, though representing 2% of the total body weight, it receives one fifth of the resting cardiac output. This blood supply is carried by the two internal carotid arteries (ICA) and the two vertebral arteries that anastomose at the base of the brain to form the circle of Willis.

Carotid arteries and their branches (referred to as the anterior circulation) supply the anterior portion of the brain while the vertebro-basilar system (referred to as posterior circulation) supplies the posterior portion of the brain.

Regulation of cerebral blood flow

Cerebral blood flow (CBF) in man is about 50 ml / 100 g of brain / minute. It has been shown that CBF, cerebral blood volume (CBV) and cerebral energy metabolism measured as cerebral metabolic rate of oxygen ($CMRO_2$) or of glucose (CMRglu) are all coupled and higher in gray than white matter. This means that the oxygen extraction fraction (OEF) remains about the same (approximately forty per cent) throughout the brain, therefore, in normal resting human brain, CBF (i.e. flow) is a reliable reflection of $CMRO_2$ (i.e. function) (Leenders et al., 1990).

CBF depends on cerebral perfusion pressure (CPP) and cerebrovascular resistance. The perfusion pressure is the difference between systemic arterial pressure and venous pressure at exit of the subarachnoid space, the latter being approximated by the intracranial pressure.

Autoregulation

It is a characteristic of the brain to adjust its own blood supply. In normal

individuals, CBF remains constant when the mean arterial pressure is between 60 and 160 mmHg, which, in normal circumstances, when the intracranial venous pressure is negligible, is the same as the CPP (Powers 1991). Whether myogenic, metabolic or neurogenic processes are responsible for this process is unknown (Aaslid et al., 1989). Autoregulation is impaired or abolished in damaged areas of the brain (e.g. by ischemia, trauma, etc.) so that CBF becomes pressure passive and follows perfusion pressure (Strandgaard and Paulson 1984 and Deardin 1985).

INTRACRANIAL PRESSURE

Once the fontanelles are closed the skull is a rigid box, which can only accommodate a limited volume. At an early age some separation of the sutures may occur.
The normal structures within the skull have more or less stable volume. There are some variations in volume depending on the person's activities, cardiovascular as well as pulmonary status. These variations are temporary and the intracranial pressure goes back quickly to its normal level.

The skull is not a completely closed sphere; there are several openings mainly in the base of the skull. It is believed that intracranial pressure is a reflection of the atmospheric pressure, which is conducted through the large neck vessels.

NORMAL INTRACRANIAL PRESSURE

The normal pressure for is 15 mmHg or 150 mm - 200 mm of water. Accurate measurement of pressure in newborn and infants is difficult to obtain but it is believed that in the first few months of life the intracranial pressure is lower. Values up to 8 mmHg have been considered to be normal in the first few months of life.

The intracranial pressure is closely related to brain perfusion. The cerebral blood flow is dependent on the intracranial pressure. In a simplified statement cerebral perfusion pressure is the difference between the systemic blood pressure and the intracranial pressure. For

this reason the intracranial pressure needs to be maintained at a steady state. This is accomplished by dynamic equilibrium of intracranial components.

As the skull is a rigid box any extra volume added to the intracranial cavity needs to be at the expense of normal intracranial components in order to maintain the intracranial pressure at a normal level.

In the early stages adjustment is made to maintain an ICP within normal range. This is called autoregulation. If the process continues the increase in volume will be associated with gradual rise in ICP. This continues up to an ICP of about 50mm Hg when the pattern changes and the intracranial cavity loses its compliance and behaves as a solid box .As seen above there will be steep rise in the curve and incremental rise of the intracranial pressure.

DYNAMICS OF RAISED INTRACRANIAL PRESSURE

Raised intracranial pressure could be the result of the following:

1. Increase of the volume of the normal content of the intracranial cavity, as increase in the volume of CSF as in hydrocephalus, increase in the volume of the brain tissue itself as in brain oedema or increased cerebral blood volume.
2. Extra volume added to the intracranial cavity as in tumors or haematomas.

Where an extra volume is added to the intracranial cavity this has to be at the expense of the normal contents. To start with the cerebrospinal fluid is squeezed out, we find that the ventricles become compressed and displaced. There will be paucity of subarachnoid spaces and the basal

cisterns become less discernible. Once a state is reached where no more CSF could be expulsed, a change in the cerebral blood flow occurs. As mentioned cerebral blood perfusion is related to intracranial pressure. With the rise of intracranial pressure there is diminished cerebral blood flow and more space is provided for the extra volume. However a state would be reached where any further decrease in cerebral blood flow would lead to cerebral ischaemia. In this situation the brain itself starts to herniate through the hiatus of the tentorium and foramen magnum. At this stage the patient's condition is precarious and needs urgent action to reduce the intracranial pressure.

Increase blood volume can occur as a result of a blockage to venous drainage from the cranial cavity or due to vasodilatation. It is very important to appreciate that cerebral blood vessels are very sensitive to changes in blood gases especially carbon dioxide. High PCO_2 results in vasodilatation and increase in cerebral blood volume.

The average brain weight varies from 1000 to 1500 grams.

MANAGEMENT OF RAISED INTRACRANIAL PRESSURE

The first step is to find the cause of the raised intracranial pressure and remove it if possible. If there is excessive cerebrospinal fluid as in hydrocephalus then shunt procedure or external drainage should be instituted. If there is a resectable tumor then this should be removed. In cases where there are no surgically treatable cause efforts should be directed at reducing intracranial pressure by one of the following means:

Osmotic Diuretic: This acts by dehydrating the brain. This is achieved by removing extra

cellular fluid by creating an osmotic gradient across the capillary wall. The most commonly used agent is Mannitol. This is a carbohydrate, which is not metabolised in the blood and remains entirely in the extracellular space. The dose is 0.25- 1 gram per kilogram body weight over 10 - 15 minutes. 20% of the solution is used. The effect of Mannitol lasts about 4 to 6 hours.

Mannitol has some side effects; its action is reduced with repeated doses and can cause systemic acidosis and renal failure due to increase plasma osmolarity. After Mannitol is stopped there is rebound of intracranial pressure.

Other diuretics used are Furosemide, which is a renal diuretic.

Diuretics could be used as a temporary measure while the patient is prepared for definitive surgical treatment.

STEROIDS

These are mainly used to reduce brain swelling around brain tumors. They are very effective in these conditions.

CSF DRAINAGE

This is an effective and rapid way of reducing intracranial pressure in cases where ventricles are visible and can be cannulated. However in severe brain oedema with collapsed ventricles it is difficult to get into the ventricle. The ventricular catheter could be used to monitor intracranial pressure at the same time.

HYPERVENTILATION

As mentioned before cerebral blood vessels are sensitive to changes in blood gases. The aim of hyperventilation is to reduce the PCO_2 to a level around 30 mmHg. Low PCO_2 will cause vasoconstriction and reduced intracranial blood volume. Levels below 30 mmHg should be avoided as it can cause cerebral ischaemia.

BARBITURATE

Barbiturate is used to induce deep coma, where there is a reduction in metabolic rate, oxygen consumption and CO_2 production. This method is used only when all other means of treatment failed.

Anesthesia for craniotomy

It is not surprising that anesthesia for craniotomy presents special considerations. The brain is enclosed in a rigid skull and the majority of craniotomies are performed for the treatment of space occupying lesions. At the same time, the brain is a highly vascular organ presenting potential for massive peri-operative hemorrhage. Tolerance of the brain to interruption of substrate delivery is minimal.

Anesthetics and physiologic factors controlled by the anesthesiologist have profound effects on the brain. Interactions between anesthesia and surgical outcome can be expected.

Preoperative evaluation

The initial approach to the patient requiring craniotomy is similar to that of all other patients. There are several additional considerations. It is important to obtain an appropriate baseline neurological evaluation. At emergence from anesthesia, failure to recover baseline neurological function can be attributed to surgery, anesthesia, or an interaction between the two. It is incumbent on the anesthesiologist to recognize changes from baseline so as

to participate in making the diagnosis. It is also important to gain insight into the magnitude of intracranial hypertension and possible interactions with anesthetic agents. Acute changes in intracranial pressure (ICP; e.g., epidural hematoma) are potentially more devastating and are likely to be more sensitive to anesthetic effects. The anesthesiologist also can benefit from appreciating the characteristics of the lesion with respect to potential for major hemorrhage.

Monitoring

For most craniotomies, monitoring consists of standard monitors in addition to an intra-arterial catheter. The arterial catheter is valuable in providing strict control of blood pressure (particularly during emergence). Central venous pressure (CVP) monitoring is usually not required for management of tumors unless the case is expected to be exceedingly long or if major hemorrhage is expected (e.g., vascular meningioma, tumor encasement of major vessels). Otherwise, indications for CVP and pulmonary artery pressure monitoring remain the same as for other patient populations dictated principally by cardiac, renal, and pulmonary status.

Use of mannitol essentially voids urine output as a monitor of intravascular volume status. The brain receives approximately 20% of cardiac output when the body is at rest. If cardiac output is approximately 5 $L \bullet min^{-1}$, it is easy to appreciate that uncontrolled hemorrhage can result in rapid exsanguination. The CVP monitor will aid resuscitation. An important reason for placement of a central venous catheter is delivery of vasoactive medications. It is sometimes difficult to predict whether the surgeon will request blood pressure to be increased (e.g., during temporary vascular occlusion of the parent vessel) or decreased (e.g., to facilitate clipping or reduce rate of hemorrhage). Delivery of drugs into the central circulation provides the fastest possible onset of action and shortens the feedback loop for dose titration facilitating exquisite control of blood pressure within the desired range.

Routine use of intra-operative electrophysiological monitoring to detect ischemia remains controversial. Although monitoring of evoked potentials makes sense, there are numerous reports of false positive and false negative readings. Some advocate use of electroencephalographic (EEG) monitoring for the purposes of pharmacologically inducing burst suppression

for neuroprotection. Efficacy is unsupported by experimental literature although the risk seems small. Monitoring of cranial nerve function is often employed during posterior fossa procedures. Implications for anesthesia largely pertain to limitation in use of muscle relaxants. Although there is no contraindication to use of relaxants during induction and positioning, it is important to assure recovery of neuromuscular function prior to surgical stimulation of the cranial nerves located in the vicinity of the lesion.

Transcranial Doppler (TCD) monitoring may be of value preoperatively in screening for vasospasm. Intra-operative use during craniotomy is cumbersome and unsubstantiated as a modifier of outcome. There is increasing hope that computerized analysis of TCD waveforms may provide useful data on intracranial pressure (ICP) and this could be useful during induction. Clearly TCD can identify complete obstruction to blood flow. More useful information regarding magnitude of ICP allowing calculation of cerebral perfusion pressure is not currently available.

Premedication

The goals of premedication in craniotomies are to avoid anxiety, provide sedation without causing respiratory depression which would cause

an increase in PaCO2 which would cause an increase in cerebral blood volume and thereby increasing ICP. In such a setting α_2 – agonists such as clonidine serve as a useful choice.

Anaesthesia induction

Concerns unique to induction of anesthesia for craniotomy are principally related to ICP in the case of mass lesions or prevention of hemorrhage in the case of vascular lesions. The history of effects of anesthetics on ICP during induction began in the 1960s when the earliest measurements were made on patients anesthetized for tumor surgery. Major increases in ICP were observed with anesthetic induction. In the subsequent zeal to provide optimal care, it was felt that any increase in ICP could only be adverse to the patient and thus use of anesthetics known to increase ICP was discouraged. Although logical, this came at some cost. Something must be used to provide anesthesia and those drugs known to reduce ICP (e.g., thiopental) typically have prolonged durations of action or produce hemodynamic instability. In fact, data relevant to effects of various anesthetics on ICP in humans is limited. Most information has been derived

from animal studies. More important, there is little data regarding any relationship between anesthetic effects on ICP and outcome from craniotomy.

Case reports in the literature showing a causal relationship between anesthetics and brain herniation on induction are almost non-existent. The one exception to this is patients with an occult lesion undergoing surgery for non-neurosurgical procedures. The vast majority of patients anesthetized for craniotomy emerge from anesthesia either with neurological status unchanged or with changes directly attributable to the site of surgery. As a result, it is difficult to advocate any specific anesthetic or technique for the purpose of induction. We do know that ICP effects of volatile anesthetics can be blunted by simultaneous moderate hyperventilation. We also know that high concentrations of volatile anesthetics perturb cerebral autoregulation. We also know that there are numerous methods to blunt hemodynamic responses to endotracheal intubation and application of the pin head-holder. Cumulatively these concerns must be weighed when inducing anesthesia for craniotomy.

With respect to cerebral aneurysms, ICP is of less concern than is prevention of abrupt and major increases in mean arterial pressure (MAP) that

may contribute to rupture of the lesion. In this case, there is abundant evidence that a poorly controlled hemodynamic state during induction is contributory. The mortality rate associated with aneurysmal rupture during induction is substantial. The goal is avoidance of hypertension. If an error is to be made it should be towards hypotension. Some advocate purposeful reduction of MAP during induction with vasodilatory agents (e.g., nitroprusside) to insure against hypertensive responses to intubation. This is usually unnecessary. Instead, controlled and progressive increases in depth of anesthesia sufficient to blunt responses to intubation are sufficient to prevent hemorrhage. This is an induction procedure that should not be rushed.

Anaesthesia maintenance

Maintenance of anesthesia during craniotomy is usually uncomplicated and generic in many respects. There are two special considerations, however. In patients with intracranial mass lesions, brain bulk can be a problem, particularly when the dura is being opened. A swollen brain can herniate through the dural defect prohibiting further dural incision. In this circumstance the anesthesiologist is frequently requested to "relax" the brain. There are multiple methods by which this can be achieved. Usually several

changes are made simultaneously which cumulatively result in improved operating conditions. The anesthesiologist can often prevent this problem during patient positioning by assuring the head is sufficiently elevated above the heart to promote venous drainage. Further head elevation intraoperatively can often cause dramatic reduction in brain bulk. This must be weighed against the risk of air embolism in which case transcardiac Doppler monitoring might be considered. Placement of the head 10–15 above the heart is usually sufficient to promote venous drainage without risk of air embolism or hemodynamic instability.

Reduction in brain bulk can also be achieved by discontinuation of inhalation anesthetics that are known vasodilators. The first drug to discontinue is nitrous oxide. It is rapidly eliminated and a greater vasodilator than isoflurane because nitrous oxide does not have compensatory reduction in metabolic rate causing coupled reduction in cerebral blood flow (CBF). Temporary discontinuation of the volatile anesthetic may also be of benefit.

There is no evidence that opioids increase brain bulk. There is evidence that opioids increase ICP. This effect, however, is modest and transient. Human study has provided convincing evidence that opioids

increase ICP as a result of effects on MAP. When autoregulation is intact, reduced MAP causes vasodilatation and a concordant increase in cerebral blood volume (CBV) and ICP. Opioid induced increases in ICP can be avoided simply by controlling MAP during opioid administration. As a result, opioids are unlikely to be an issue during maintenance with respect to brain bulk.

Mannitol reduces brain bulk by creating an osmotic gradient across the blood brain barrier causing water to flux from the extracellular extravascular to intravascular compartments. There also is evidence that mannitol improves deformability of red blood cells, thereby reducing viscosity promoting increased blood flow. As a result, autoregulation causes vasoconstriction that may reduce CBV. Mannitol is best given around time of skin incision (typically 0.5 $mg \bullet kg^{-1}$) so the peak effect becomes available upon dural opening. Additional mannitol may be of value if the brain is still "tight".

If hypercapnia is present it should be corrected. The response of the cerebral vasculature to changes in $PaCO_2$ is rapid. There has been a major shift in attitude regarding the value of hypocapnia with the preponderance of

opinion being that a major reduction in $PaCO_2$ poses the risk of secondary ischemic injury. Stabilizing the $PaCO_2$ in the range of 30–35 mmHg is usually adequate.

Administration of thiopental in large doses cause major reduction in metabolic rate and a coupled reduction in CBF. This can be effective but will likely prohibit adequate neurologic evaluation upon emergence.

Lumbar cerebrospinal fluid (CSF) drains are often placed for aneurysm surgery. The volume drained often exceeds 100 mL making this technique perhaps the most effective in reducing brain bulk of all options. The goal in aneurysm surgery, however, is different from that of tumor surgery. In most aneurysm cases, reduction in brain bulk is performed to reduce the magnitude of retractor pressure required to expose the aneurysm at the base of the brain. CSF drainage is usually not employed until after the dura is opened. This is because rapid and profound reduction in brain bulk can tear veins draining into sinuses. An acute subdural hematoma can be formed if the drain is opened prior to surgical exposure of the brain with little hope of prompt hemostasis. Practical approaches to this is to ensure patency of the drain after positioning by observing progression of the air/fluid level

through the connected catheter (usually less than 1 mL of CSF drainage is required to confirm this) and then leave the drain closed until surgical requirements dictate that it be opened. CSF drains are rarely used for most types of tumor surgery because of fear of transtentorial herniation. Occasionally CSF drains are placed for transphenoidal pituitary surgery, not to drain CSF, but to allow injection of saline or air to force the tumor towards the sphenoid sinus to facilitate surgical excision.

Management of ventilation

The classic reflex when confronting a patient with intracranial hypertension is use of hyperventilation. This is derived from knowledge that alteration of $PaCO_2$, within the range of approximately 20–80 mmHg, causes parallel changes in CBF. CBF, in fact, is only a surrogate for the true determinant of ICP, that being CBV. CBF is easy to measure while CBV is not (particularly in humans). It is logical, however, that given a constant MAP, $PaCO_2$ induced changes in CBF should correlate with cross-sectional diameter of the cerebral arterial vasculature. Decreasing $PaCO_2$ results in decreased CBF and it is presumed that this also causes decreased CBV. Indeed, there is abundant clinical evidence in patients with ICP monitors in

place, that reduction of $PaCO_2$ results in at least transient reduction in ICP. Neuroanesthetic practice, therefore, had been to cause large reductions in $PaCO_2$. Data from head injury patients has caused a major change in this perspective. Use of retrograde jugular venous hemoglobin-O_2 saturation measurement techniques has repeatedly shown that reduction in $PaCO_2$, in fact, can exacerbate cerebral hypoperfusion. As a result, it is no longer advocated that major reductions in $PaCO_2$ be made in patients undergoing craniotomy for space occupying lesions. Modest reductions in $PaCO_2$ remain valuable, however, to counteract vasodilatory effects of volatile anesthetics.

It is also important to recognize the value of end-tidal CO_2 monitoring during craniotomy. This advance has reduced the need for repeated arterial blood gas sampling. However, analysis of arterial to end-tidal CO_2 gradients in neurosurgical patients has shown that the gradient is not always predictable and should be measured for the individual patient when management of intracranial hypoperfusion is a concern.

Muscle relaxants

Several muscle relaxants have received special consideration in the context of craniotomy. The most interesting is succinylcholine. There is

clear evidence from both experimental animals and humans that succinylcholine can increase ICP under conditions of intracranial hypertension. The magnitude of increase is typically small and transient. The mechanism was originally thought to be attributable, not to succinylcholine, but rather preservatives used in its formulation. It has been shown in humans that ICP changes caused by succinylcholine can be blocked by pre-administration of a defasciculating dose of non-depolarizing relaxants. This suggests that fasciculations resulting from succinylcholine play a role in the ICP effects of this drug. A probable mechanism is the massive fasciculation-induced afferent barrage from muscle spindles to the brain that cause transient increases in metabolic rate and coupled increases in CBF. Common sense plays a major role in the decision whether to use succinylcholine in patients with intracranial hypertension. Pretreatment with a small dose of a non-depolarizing agent most likely makes the argument moot. At the same time, emergency airway management and the clear desire to minimize hypercapnia and hypoxemia in patients with traumatic brain injury (TBI) dictate that succinylcholine can be an appropriate adjunct for tracheal intubation until a relaxant with similar speed of onset and duration of action is introduced to clinical practice.

There is clear evidence that the duration of action of non-depolarizing muscle relaxants are reduced by a variety of anti-convulsant medications. Even short durations of exposure to anti-convulsants can elicit this change. The mechanism for this remains unclear. Most patients requiring craniotomy are being treated with anticonvulsants. As a result, the non-depolarizing relaxant dosing regimen will, probably, require alteration. Atracurium and cis-atracurium seem to be largely resistant to these effects, most likely because metabolism is achieved by Hoffman elimination.

Management of temperature

There has been abundant enthusiasm over the past decade for routine use of intra-operative hypothermia in patients requiring brain surgery. This is based on overwhelming laboratory evidence that reduction of body temperature by even 2–3°C can cause major neuroprotection. Several problems remain before strong advocacy can be made for routine practice of induced hypothermia. First, there is virtually no evidence of mild hypothermia efficacy in humans. An appropriately powered trial in patients (with TBI) failed to define benefit and in fact identified worsened outcomes in the elderly. Despite considerable effort, there remains no clear evidence

that induced hypothermia is neuroprotective in cardiac surgical patients. Finally, there is increasing evidence that mild hypothermia poses a variety of risks to the general surgical population. The International Hypothermia Aneurysm Surgery trial is currently being conducted with 1,000 patients being randomized to normothermia (36.0–37.0°C) or hypothermia (32.5–33.5°C) during intracranial aneurysm surgery.

Pharmacological neuroprotection

A holy grail of academic neuroanesthesia has been the demonstration of neuroprotective efficacy of anesthetics and other purported neuroprotective compounds. The simple interpretation of four decades of research is that we still lack definitive proof (particularly in humans) that pharmacological neuroprotection is a reality. Because most anesthetics reduce brain metabolic requirements, it certainly makes sense that in the context of diminished substrate supply anesthetics will increase tolerance to ischemia. However, the issue is now recognized to be far more complex than this logic. More important, other than a few studies examining barbiturates in cardiac surgical patients, there are no human studies that have prospectively defined presence or absence of neuroprotection from anesthetics.

Laboratory studies have now irrefutably shown that anesthetics increase tolerance of brain to ischemia. This is independent of the type of ischemia (global *vs.* focal). The mechanisms are likely related to inhibition of glutamatergic (excitatory) neurotransmission and potentiation of GABAergic (inhibitory) neurotransmission. Many anesthetics meet these criteria (i.e., volatile agents, propofol, barbiturates). Other compounds such as nitrous oxide and opioids appear to be inert. It is clear that animals sustaining stroke while awake have larger resultant lesions than if anesthetized. But which anesthetic is superior to another remains controversial. Many clinicians persist in use of thiopental as a first line agent. The logic for this is that thiopental has the longest track record of experimental efficacy and there is one human cardiac surgical trial that found benefit (albeit small). It is difficult, therefore, to recommend one agent as being superior to the others. There is one exception to this conclusion and that is etomidate. Although outcome evidence is not available, human studies have provided reasonable evidence that etomidate may exacerbate injury.

As a result of incomplete science regarding anesthetic efficacy in humans, and in the absence of any other drugs approved for the purpose of

neuroprotection in humans, the anesthesiologist is left with a speculative practice when providing pharmacological neuroprotection. Perhaps the best we can do for the patient, with certainty, is to provide oxygenated blood at a sufficient perfusion pressure with simultaneous control of temperature and glucose concentration.

Management of emergence

If failure to emerge is attributable to surgery, a computerized tomographic scan is usually performed to rule out hematoma formation. In contrast, if the problem is anesthesia based, patience in allowing elimination of anesthetic agents (or use of opioid antagonists or reversal of neuromuscular blockade) is the solution and the surgeon should be counseled that anesthesia is a likely explanation. Therefore, when planning the anesthetic, it is helpful to restrict use of agents to those that can be monitored for concentration or those for which sufficient knowledge of pharmacodynamics allows highly probable clearance by the time emergence is desired. As an example, induction doses of thiopental or propofol are unlikely to relate to failure to emerge from a three- to four-hour procedure. In contrast, persistent blood

propofol concentrations sufficient to prevent awakening after a prolonged infusion may be difficult to diagnose.

Neuromuscular blockade is maintained until completion of the head dressing. Elimination of volatile anesthetics can be initiated at the time of bone flap replacement. Anesthesia is maintained by either residual concentration of opioid (i.e., fentanyl or sufentanil) or continued infusion of remifentanil. Supplementation with nitrous oxide is likely superior over use of *IV* agents because its concentration can be defined by end-tidal gas analysis, which aids in defining failure to emerge. Rapidly cleared IV agents such as lidocaine can be of value in sustaining anesthesia for a few additional minutes. If remifentanil is used, the rate of infusion can remain unchanged until the dressing is complete. This supports anesthesia during placement of the dressing but still allows a prompt and reliable emergence. It is important, however, to provide transitional analgesia before discontinuation of remifentanil. Administration of 10 mg morphine or 100–150 μg fentanyl (in adults) is usually sufficient to provide analgesia without altering predictability of emergence.

Patients undergoing craniotomy may exhibit hypertension during emergence that is sustained through the early phases of recovery. Because of the implications of intracranial hemorrhage, it is imperative to plan for treatment of hypertension before it becomes manifest. Prophylactic doses of labetolol are helpful, usually requiring 40–60 mg to be effective. It has not been proven that emergence hypertension contributes to hematoma formation. It has been shown, however, that many patients who develop postoperative haematomas have had episodes of hypertension during emergence or early recovery. The source of hemorrhage is almost always within the surgical field and thus quality of hemostasis undoubtedly is important. However, because the mortality associated with postoperative hematoma formation requiring emergent evacuation is high, it seems incumbent on the anesthesiologist to seriously attend to management of hemodynamics during emergence.

α_2-Adrenoceptor pharmacology

Awakening of interest in a sub classification of α-adrenoceptors was foreseen in 1969 as a means to explain the regulation of the release of nor- adrenaline, from which it was inferred that a α-receptor was located presynaptically. This led to a reclassification of α-adrenoceptors, based on their synaptic location, into postsynaptic α_1, and presynaptic α_2. As more selective α-adrenoceptor antagonists became available it was possible to separate the α-adrenoceptors into two subtypes based on the receptor response to the antagonists prazosin (α_1) and yohimbine (α_2). This classification was further expanded as the result of radioligand binding and molecular biological techniques.

Adrenoceptor ligand techniques have at present identified four α_2-isoreceptors. Kobilka et al and Regan et al cloned the genes encoding α_2-adrenoceptors from the human platelet and the human kidney and produce functional α_2-receptors. The α_{2A}-receptor corresponds lo the platelet α-receptor, which has been gene mapped to chromosome 10. The kidney isoreceptor maps to chromosome 4.

It seems that the anaesthetic effects of α_2-agonists are subtype-specific. Although the adrenoceptor subtype transducing the central hypnotic action has not yet been identified, radioligand techniques have identified the receptor subtype in human spinal cord as α_{2A} . Millan showed that specific α2A antagonists only reversed the analgesic effects of α2A-agonists in the spinal cord.

The α_2-adrenoceptor is a member of the family of G coupled membrane receptors. The subtypes of the adrenoceptors are homologous in that they have a common long chain of

amino acids between 415 and 480 amino acids in length, with seven transmembrane hydrophobic domains that are connected by loops which project into either the cytoplasm or the extracellular space and straddle the lipid membrane. Affinity labeling studies with α_2-adrenergic receptors employing antagonist and agonist ligands suggest that it is the fourth membrane-spanning domain, which is involved with ligand binding. Differentiation of α_1 from α_2-receptors depends on the configuration of the rather shorter cytoplasmic tail.

α_2-adrenoceptors activate the G_i protein, which carries the suffix i because it inhibits adenylyl cyclase and so prevents an increase in cyclic adenosine monophosphate (cAMP) levels. The activated α_2-adrenoceptor produces its effects by at least five different mechanisms, the main one being the inhibition of adenylyl cyclase and the decrease in cAMP levels. This may however be only a permissive role as the decrease in cAMP alone is not adequate to produce many of the effects of the α_2- agonists. The extrusion of protons is increased by accelerating Na^+/H^+ exchange in the platelet by α_2-receptor activation; calcium entry into nerve channels may be decreased and phosphatidyl inositol metabolism may be affected. The inhibitory (G) protein can also activate a variety of ion channels, such as the K^+ channel in cell membranes. Evidence that dexmedetomidine acts by modifying the function of K^+ channels is based on the ability of pertussis toxin (a selective inhibitor of the G_i protein) or 4-amino pyridine (which blocks the K channel) to inhibit the effects of dexmedetomidine in a dose- dependent manner.

Clonidine

Clonidine is the prototype α_2-adrenoceptor agonist which has been extensively studied in animals and humans, but it is only a Partial agonist with a ratio of 200: 1 ($\alpha_{2:}$ α_1) its

action is limited at higher doses by the ceiling effect. Clonidine is an imidazoline compound. Receptors distinct from the α_2-receptor, which bind imidazolines and oxazolines (e.g. idazoxan and rilmenidine) have been identified. These receptors have been named the I receptors and classified into two subtypes — I_1 and I_2. I_1 receptors appear to be confined to the brain, whereas I_2 receptors are found in the brain, in the pancreas (activated by a K^+ channel, and involved in insulin release) and in the kidney. Many drugs act on the α_2-receptor and the I_1 receptor to a greater or lesser extent those having a predominant effect on the I_1 receptor (clonidine < moxonidine < rilmenidine) produce centrally mediated hypotension, but the I_1 agonists do not produce sedation.

Clonidine can be administered orally, intravenously, intramuscularly, transdermally, epidurally and intrathecally. Clonidine is lipid-soluble, rapidly absorbed orally, and reaches a peak plasma level within 60—90 mm. The elimination half-life is 9—12 h; about 50% is metabolized in the liver to inactive metabolites, and the remainder is excreted unchanged in the kidney.[3]

Dexmedetomidine

Dexmedetomidine is a more selective and specific α_2-adenoreceptor agonist than clonidine, with an affinity for the α_2-adrenergic receptor eight times that of clonidine,[59]

-although even it may bind to α_1-adrenoceptors at very high doses and attenuate its α_2 action. Dexmedetomidine is the dextrostereoisomer and pharmacologically active component of medetomidine, which is used in veterinary practice; both drugs are imidazoles. Dexmedetomidine is a potent drug and produces significant effects at plasma concentrations of less than 1.0 ng/ml. Its volume of distribution and clearance are similar to those of fentanyl,

although its pharmacokinetics is complex; dexmedetomidine exhibits a concentration-dependent non-linear pharmacokinetic profile.[61] At high concentrations its volume of distribution is decreased due to peripheral vasoconstriction, therefore intravenous dexmedetomidine should not be given rapidly. An oral preparation given to animals avoids the transient rise in blood pressure that occurs after intravenous injection of dexmedetomidine in some animal studies and in humans.[5] A sublingual preparation is not yet available but would allow preoperative administration, without he discomfort of an intramuscular injection or the uncertain absorption of an oral dose.

Mivazerol

Mivazerol is the most recent α_2-agonist to be used clinically, and is currently being assessed for its anti-ischaemic effects rather than its sedative or anaesthetic effects.[20]

Reversal

The anaesthetic action of the α_2-adrenoceptor agonists can be reversed by centrally acting α_2-antagonists such as atipamezole and idazoxan, but not by peripheral α_2-antagonists that do not cross the blood brain barrier. α_2-antagonists are not yet routinely used in human anaesthesia, but atipamezole has been tested in human volunteer clinical trials and well tolerated.[35]

Sites of action

The use of radioligands has allowed auto radiographic mapping of the locations of α_2-adrenoceptors within the central nervous system. The locus coeruleus in the upper brainstem has been identified as a major site for the hypnotic action of the α_2-agonists. The locus coeruleus

(LC; sky-blue spot) is a small but very important neuronal nucleus situated bilaterally in the floor of the fourth ventricle. It has major afferent connections from the rostral ventrolateral medullary nuclei. It has three important sets of efferent connections:

I. Noradrenergic fibers, which connect with the subthalamic, relay nuclei and the thalamus, with consequent effects on cortical activity.

2. Fibres to the descending reticular formation with connections to the pressor and depressor areas of the vasomotor centers.

3. Descending fibers in the reticulospinal tracts, which inhibit pain transmission at a spinal level.

The rate of spontaneous discharge of the LC neurons correlates with the level of arousal and vigilance, and is lowest during rapid eye movement sleep. Opioids acting through μ-receptors and α_2-adrenoceptor agonists hyperpolarize and silence LC neurons, the former acting through chloride channels and the latter through potassium channels sensitive to suppression by pertussis toxin producing in animals a dose-dependent state resembling sedation and anaesthesia. Clonidine markedly decreases the noradrenaline concentration in the LC. Dexmedetomidine injected directly into the LC produces a dose- dependent hypnotic response in awake rats, while injections made 2 mm lateral to the LC had no effect. If the α_2-adrenoceptor subtype in the LC can be identified, more specific drugs could be developed and targeted at the desired effects of sedation and anaesthesia.

High densities of α_2-agonist binding sites have been observed in the dorsal motor nucleus of vagus nerve which may be the site of the bradycardic and hypotensive effects of the α_2-agonists, although other studies suggest that these receptors are more susceptible to agonists with an imidazoline structure (e.g. clonidine) than to catecholamines.

In human spinal cord high densities of α_2-adrenoceptors have been shown in the intermediolateral cell column and the substantia gelatinosa.

Mechanisms of analgesic action

α_2-Adrenoceptors are found postjunctionally on the dorsal horn neurons of the spinal cord and may act by inhibiting the release of neurotransmitters such as substance P. Noradrenergic neurons in several brainstem nuclei descend to these dorsal horn neurons; nociceptive signal transmission by this pathway can be inhibited by the application of α_2-agonists centrally to the brainstem nuclei. Other mechanisms of analgesic action by the α_2-adrenoceptor agonists may include interaction with cholinergic, purinergic and serotonergic pain systems.

Radioligand studies have shown that μ opioid receptor distribution overlaps that of α_2-adrenoceptors in the dorsal horn area and in the LC. This relationship appears to be functional as well as anatomical as there is a great deal of evidence, both experimental and clinical, to show that α_2-agonists and opioids given together into the spinal cord act synergistically to reduce pain. Co administration of low doses of dexmedetomidine and morphine (μ-agonist) produce a synergistic inhibition of C-fiber responses but not Aβ-fibre evoked responses, suggesting that the interaction is selective to afferent pain fibers, presynaptic to the dorsal horn neurons. The synergism is mediated through the μ opioid receptor but not the δ-receptor and can be reversed by either naloxone or atipamezole. The mechanism of synergism may be through some sort of convergence of each receptor type on G protein- mediated second messenger channels able to regulate K^+ and or Ca^{2+} channels.

Receptor interactions

The α_2-agonists and the benzodiazepines both produce sedation and anxiolysis. The effect of these drugs when administered together is greater than that expected from an additive response. Application of specific antagonists (atipamezole — dexmedetomidine and flumazenil — midazolam) does not reverse the action of the other class of drug. It is unlikely that this synergism is due to a drug kinetic effect or to direct receptor interaction; it seems it is exerted at a pre- or post receptor locus.

The α_2-adrenoceptor agonists also interact with transmembrane calcium movement. Verapamil, a calcium-channel blocker, significantly enhanced the duration of the hypnotic—anaesthetic action of dexmedetomidine, while a calcium-channel agonist (BAY K8644) reduced the hypnotic—anaesthetic properties of dexmedetomidine. The interaction between the α_2-agonists and calcium- channel blockers may be due to co activation of different subtypes of calcium channel.

Physiological effects of the α_2-adrenoceptor agonists

Central nervous system

The α_2-adrenoceptor agonists produce dose-related sedation, anxiolysis, analgesia, and a reduction in the requirements for other anaesthetic agents. They also reduce intraocular pressure.

Respiratory effects

The effects of the α_2-adrenoceptor agonists on the respiratory system appear to be mild. Infusions of increasing levels of dexmedetomidine in healthy volunteers produced dose-related sedation and sleep, with a slight increase in $Paco_2$,a decrease in minute ventilation

characterized by a reduction in tidal volume and little change in respiratory rate. No significant oxyhaemoglobin desaturation occurred. At all dose levels up to 2 μg kg^{-1} the hypercapnic ventilatory response slope was decreased slightly; there was an unexplained initial increase in oxygen consumption. In dogs an initial dose of dexmedetomidine 1 μg kg^{-1} decreased resting ventilation but higher doses progressively increased resting ventilation even though the hypercapnic ventilatory response was decreased at doses higher than 10 μg kg^{-1}. Nebulized clonidine has been shown to reduce bronchoconstriction produced by histamine in asthmatics.

Cardiovascular responses

Postjunctional α_2-adrenoceptors are located on human resistance and capacitance vessels where they mediate constriction. The effects of α_2-constriction differ from α_1 effects in that they are slower in onset, longer-lasting, and more sensitive to pH and temperature changes and may require angiotensin II for their expression. Pressor responses to α_2-agonists are more sensitive to blockade by calcium antagonists than those induced by α_1-agonists, as α_1 activation not only produces extracellular calcium influx, but also induces intracellular calcium release.[31]

Two predominant haemodynamic effects occur when α_2-agonists are given intravenously. There is an initial short-lived increase in blood pressure, systemic vascular resistance and a concurrent decrease in cardiac output due to activation of the Postjunctional α_2-receptors on the peripheral vasculature. This is accompanied by a decrease in heart rate, and followed by a longer-lasting decrease in blood pressure and heart rate resulting from a centrally mediated decrease in sympathetic tone and an increase in vagal activity.[14]

The exact site of action for the central hypotensive effect is not yet known. There are α_2-receptors in the nucleus tractus solitarius and the lateral reticular nucleus, and the pressor

response mediated by the LC is inhibited. Clonidine has little effect on blood pressure in hypertensive tetraplegic patients in whom central sympathetic control has been lost. The hypotensive action of the α_2 agonists is not attenuated by depletion of catecholamines within the brain, suggesting that the hypotensive effect is a direct postsynaptic α_2 action. It seems that the imidazole-preferring receptors are important in mediating the hypotensive effects of the α_2-agonists. The α_2-agonists appear not to affect baroreceptor reflex gain, but to reset them to operate at a lower blood pressure level.

There is evidence to suggest in experimental animals that the bradycardia is mainly produced by a central action of the α_2-agonists: L659,O66 an α_2-antagonist that does not cross the blood brain barrier, reversed the hypertensive response to dexmedetomidine infusion but had no effect on the reduction in heart rate, while atipamezole, an α_2-antagonist that does cross the blood brain barrier, reversed the effects of dexmedetomidine on heart rate. There may also be a vagomimetic effect or a presynaptically mediated reduction in noradrenaline release, as the bradycardiac effect is sustained in tetraplegic patients.[34]

Although the α_2-agonists can cause bradycardia, they can protect against other arrhythmias; dexmedetomidine prevented adrenaline-induced arrhythmias in dogs anaesthetized with halothane.

Coronary vasculature

Application of α_2-adrenoceptor agonists to coronary may cause vasoconstriction maximized by inhibition of nitric oxide synthesis by N^G nitro-L-arginine methyl ester (L-NAME). The α_2-adrenergic antagonist atipamezole blocked the contractile response to low

concentrations of dexmedetomidine in proximal but not distal coronary artery. suggesting predominance of α_2 receptors proximally. Experimental work in animals may not be applicable in humans as there is considerable interspecies variation in the existence and distribution of α_2-isoreceptors in the coronary circulation.[43]

There are no postsynaptic α_2-adrenoceptors in the myocardium but there are presynaptic α_2-receptors modulating noradrenaline release. Information derived from the responses of isolated ventricular myocardium suggests that the decrease in cardiac output seen after the infusion of α_2-agonists is not due to an intrinsic myocardial contractile action but secondary to the increase in systemic vascular resistance produced by peripheral α_2 vasoconstriction.[43]

Effects on cerebral blood flow and intracranial pressure

Both cerebral blood flow (CBF) and cerebral metabolic rate of oxygen consumption (CMRO2) decreased when dexmedetomidine was given during halothane anaesthesia in mechanically ventilated dogs. Similar responses were found when dexmedetomidine was used with isoflurane, although $CMRO_2$ did not change. In neither study was there evidence of global ischaemia. In both studies dexmedetomidine reduced MAC; therefore one mechanism of the reduction CBF may be prevention of the vasodilating effect of the volatile agents. An increase in cerebrovascular resistance mediated through the postsynaptic α_2-receptors is also possible.[46]

Endocrine effects

Insulin release is inhibited by a direct action on the β-cells of the islets of Langerhans. Although hyperglycaemia has been reported in animals given α_2-agonists, in

humans this does not appear to be a clinical problem. The release of growth hormone is enhanced and lipolysis in adipose tissue is inhibited. Those α_2-agonists with an imidazoline structure can inhibit steroidogenesis.[4]

Renal effects

Diuresis is a noticeable effect of the α_2-agonists produced by a variety of mechanisms, although the relative importance of each is not yet clear. Clonidine inhibits the release of antidiuretic hormone in dogs and decreases the levels of vasopressin in human cerebrospinal fluid. The renal tubular action of antidiuretic hormone is blocked by α_2-agonists and there may also be an increase in glomerular filtration rate. Azepexole inhibits the release of renin through receptors on the juxtaglomerular apparatus in an isolated perfused kidney. Another mechanism of action that has been investigated is the release of atrial natriuretic factor.

Other important physiological actions

They produce dry mouth due to reduced salivation. There is a decrease in vagally mediated bowel motility and secretion throughout the gastrointestinal tract although there is no effect on gastric pH. Clonidine has been used to teat watery diarrhea. The α_2– adrenoceptors on human platelets have been implicated in platelet aggregation.

Alpha 2 Adrenergic Agonists and Anaesthesia

Introduction

The anaesthetic use of α_2-adrenergic receptor agonists has been of considerable and sustained interest for the last 15 years. Clonidine, the archetype but not the most selective, is nowadays familiar to many anaesthetists. The different sedative, haemodynamic and analgesic properties of these agents is however confusing and the exact role of α_2-adrenergic receptor agonists and especially clonidine, remains a matter of debate and poorly defined despite considerable clinical evidence (1). Based on this evidence we can nevertheless identify when α_2-adrenergic receptor agonists can be valuable in perioperative management.

α_2- adrenergic agonists cause

1.dose related sedation

2.anxiolysis

3.reduction of secretions

4.peri operative hemodynamic stability

5. analgesia

6.reduction in requirements for opioids and other anaesthetic agents

Premedication

α_2-adrenergic receptor agonists cause sedation by stimulation of the locus coeruleus, a nucleus of the medulla involved in the sleep-wake cycle (2). Sedation is by stimulation of specific α_2 adrenergic receptors coupled with a G protein, leading to cell membrane hyperpolarisation. The sedative effect of α_2-adrenergic agonists is antagonised by α_2 adrenergic agonists, explaining why less selective agents, such as clonidine, which has some a1 stimulatory activity, do not achieve complete anaesthesia. Because of their sedative effect, α_2-adrenergic agonists can be used as premedicants and, in addition, can have an anaesthetic-sparing effect during anaesthesia. α_2-adrenergic agonists reduce the dose of intravenous hypnotic needed for anaesthetic induction and orotracheal intubation, and reduce the MAC of co-administered volatile anaesthetic agents.[49] Sedation is associated with mild respiratory depression, which might be more serious in high-risk patients. Clonidine has been recommended as premedication in a dose of 1-3 mcg/kg. Dexmedetomidine is a more selective α_2-adrenergic agonist with the same effects and a marked anaesthetic sparing effect during surgery.[62] If induction agent doses are not reduced, both drugs may cause hypotension at the induction of anaesthesia, and increase the incidence of bradycardia during anaesthesia. Because of these side effects, some anaesthetists are reluctant to give α_2-adrenergic agonists as premedication. There are some exceptions where they could be very suitable:

• Drug addicts and alcoholics give problems such as withdrawal symptoms, and the risk of increased sympathetic activity in cocaine users. Sympathetic hyperactivity caused by cocaine is well controlled by α_2-adrenergic agonists. Clonidine is a classic treatment for opioid and alcoholic withdrawal. Given as premedication and continued after operation, α_2-adrenergic agonists reduce the risk of withdrawal.[7]

• Chronic pain and palliative care patients are often receiving large doses of opioids and have greater perioperative opioid needs, that can be markedly reduced by α_2-adrenergic agonist premedication.

• Hypertensive patients are particularly vulnerable to swings in blood pressure during surgery and premedication with α_2-adrenergic agonists is a useful, and under-utilised, means of reducing this hyper-reactivity. Obviously those few patients still receiving long-term treatment for hypertension with α_2-adrenergic agonists must not have it stopped peroperatively. In such patients clonidine forms an essential part of their premedication.

Control of haemodynamic instability and prevention of myocardial ischaemia and related cardiac complications

The haemodynamic effects of α_2-adrenergic agonists are both peripheral and central. Stimulation of subendothelial receptors causes vasoconstriction.

Conversely, stimulation of α_2-adrenergic receptors of neurons in the nucleus tractus solitarius augments the inhibition by this nucleus of the sympathetic neurons of the medulla. In this way, alpha adrenergic agonists reduce the tonic activity of the baroreflex, decreasing arterial pressure and causing bradycardia. On the other hand the phasic activity of the baroreflex is preserved or even improved, so that any decrease in arterial pressure is followed by a significant increase in heart rate and any increase in arterial pressure is better controlled by a consequent bradycardia. In addition, α_2-adrenergic agonists depress presynapic sympathetic neurons in the lateral horn of the thoracic spinal cord. This effect is reversed by the local administration of cholinesterase inhibitor neostigmine. Consequently, intrathecal administration of α_2-adrenergic agonists causes more marked hypotension than parenteral administration.

Finally, hypotension and bradycardia induced by α_2-adrenergic agonists are reversed by ephedrine and atropine respectively but large doses are required.

In both healthy volunteers and patients, α_2-adrenergic agonists decrease plasma catecholamine levels. Giving α_2-adrenergic agonists before anaesthesia decreases cardiac output, vascular resistance, cardiac preload, afterload and contractility. Conversely, during anaesthesia, clonidine or dexmedetomidine increase cardiac output by improving cardiac loading conditions. In addition α_2-adrenergic agonists prevent hypertension and tachycardia on intubation and during surgical stimulation. However hypotension and bradycardia occur more frequently in patients after clonidine, dexmedetomidine or mivazerol. During recovery from anaesthesia, these agents prevent tachycardia and hypertension, decrease the incidence of shivering, and reduce VO2. Given as 50 mcg doses, a dose of up to 150 mcg will suppress postoperative shivering in approximately 90% of cases in less than 5 minutes. Clonidine, dexmedetomidine and mivazerol, in patients at risk during cardiac or vascular surgery, may provide better haemodynamic control and prevent myocardial ischaemia. In patients such as those with documented coronary artery disease undergoing vascular surgery, mivazerol reduces cardiac morbidity and mortality.

Postoperative analgesia and regional anaesthesia

α_2-adrenergic agonists inhibit transmission of nociceptive stimuli in the dorsal horn of the spinal cord. Their effect mimics that of noradrenalin released by inhibitory descending pathways. Noradrenaline inhibits the evoked activity of wide dynamic range neurons and causes analgesia in laboratory animals. Moreover α_2-adrenergic agonists increase the analgesic effect of opiates and interact with cholinergic neurons to do so. They augment local anaesthetic blockade and prolong duration. Clonidine has been used by epidural, spinal,

perineural, intra-articular and parenteral routes to obtain postoperative analgesia.

Central Nerve Blocks

Because of its analgesic action in the spinal cord, clonidine was initially given either by the epidural or intrathecal routes. Epidural or intrathecal clonidine is not neurotoxic and thousands of patients have received the drug by these routes without neurological complication. However, because of the large epidural doses that are necessary to obtain long-term analgesia (up to 2-3000 mcg per 24 H for the epidural route!) sedation, hypotension and bradycardia are common. The use of epidural clonidine as the sole analgesic agent is thus not popular, and combination of epidural clonidine with either opioids and / or local anaesthetics is more commonly used for postoperative analgesia. Even here, the dose should be limited to between 10 and 15 mcg/kg/hour to avoid side effects.[24]

Compared with morphine, intrathecal clonidine produces analgesia of shorter duration but without the associated risk of respiratory depression or urinary retention. In association with local anaesthetics the maximum dose of intrathecal clonidine is 1 mcg/kg. Giving clonidine with a local anaesthetic improves the quality and duration of the block, minimises the pain of the tourniquet during lower limb surgery, and prevents shivering. The quality of spinal anaesthesia during lower limb orthopaedic surgery using a tourniquet is considerably improved and prolonged by adding of clonidine to the local anaesthetic solution. Caesarean section under spinal anaesthesia is another good indication for intrathecal clonidine.

Caudal clonidine combined with local anaesthetics in children is potentially very useful and increases the duration of anaesthesia and analgesia by a factor of 2 or 3 without haemodynamic side effects. The dose is between 2 and 3 mcg/kg.[26]

Either epidural and intrathecal clonidine have been suggested for alleviation of labour pain, with clonidine given either alone or in combination with intrathecal sufentanil or epidural bupivacaine. Clonidine crosses the placenta but no adverse effect has been documented in the new-born. To avoid hypotension and bradycardia in the mother and in the foetus as well, the dose of clonidine must be limited to 100 mcg during labour.

Peripheral Nerve Blocks

Clonidine is commonly used as an adjuvant to local anaesthetics in peripheral nerve blocks where it prolongs the duration of anaesthesia and analgesia. This effect is obtained at relatively small doses (75 to 150 mcg) so the risk of side effects. Adding clonidine gives very good quality of analgesia after surgery with a duration of over 24 hours for some lower limb blocks. However, there is a risk of prolonged motor block, particularly in the elderly patient, which could prevent mobilisation.[28]

The quality of intravenous regional anaesthesia produced by lidocaine is improved by 150 mcg of clonidine particularly tolerance of the tourniquet.

Intra-articular analgesia has gained in popularity in recent years, particularly with the greater number of arthroscopies. performed. Intra-articular clonidine produces analgesia similar to intra-articular morphine.[29]

Thus, clonidine is nowadays used widely as an adjunct to local anaesthetics in peripheral blocks, and its use for intravenous regional anaesthesia or intra-articular analgesia appears promising.

Applications in specialized surgery

The effects of the α_2-agonists may be particularly useful for certain types of surgery where hypotension or a decrease in intraocular or intracranial pressure is desirable.

Clonidine causes direct vasoconstriction of afferent arteries of the ciliary process resulting in decreased production of aqueous humour, and also increases outflow of aqueous humour by decreasing vasomotor tone of the aqueous drainage system, especially in glaucoma. Clonidine has been shown effectively to reduce intraocular pressure and anxiety and to speed recovery in patients undergoing intra-ocular surgery. A single intravenous dose of dexmedetomidine (0.6 μg kg^{-1}) reduced intraocular pressure by 34%; after intubation the intraocular pressure was 27% less in the dexmedetomidine-treated group compared with the placebo group. Catecholamine concentrations and blood pressure were also significantly reduced in the dexmedetomidine group.

Dexmedetomidine (1.0 μg kg^{-1}) given intramuscularly as premedication produced sedation and a significant reduction in intraocular pressure with minimal haemodynamic side effects for day-case cataract surgery performed under regional anaesthesia

Oral clonidine premedication (4-6 μg kg^{-1}) reduced bleeding and improved surgical conditions for middle ear surgery.

α_2-Adrcnoccptor agonists may be beneficial in patients with intracranial pathology as maintenance of haemodynamic stability and avoidance of hyperdynamic episodes is_important. The α_2-adrenoceptor agonists may reduce intracranial pressure and offer_protection during cerebral injury. They reduce intracerebral blood flow; one mechanism of action may be by reducing requirements for volatile agents and thereby avoiding the vasodilatation induced by them. As yet, there are no clinical studies on changes in intracranial pressure or cerebral protective effects of the α_2 agonists. Chadha *et al.* reported that oral clonidine pretreatment reduced the haemodynamic responses to surgical stimuli during craniotomy.[3] Although another study was less convincing the potential to antagonize the effects of the $\alpha_2$agonists with specific α_2-antagonists may be useful in neurosurgical anaesthesia where prompt awakening is needed.

Qualifications for inclusion into the neuroanesthesia drug club:

1.Controllability. (e.g. rapid onset and offset of effect)

2.Stability of intracranial homeostasis.

3.Hemodynamic stability.

4.Noninterference with neurophysiologic monitoring.

5.Neuroprotection.

6.Antinonociception.

Anaesthetic sparing

In animals clonidine reduces MAC by up to 50%, whereas dexmedetomidine reduces

MAC by more than 90%. Too little is known as yet about the action of dexmedetomidine at high doses in humans to make it likely that it will be used as an anaesthetic agent in its own right in the near future. However, it has already been shown to have significant anaesthetic sparing effects in clinical studies.

In patients undergoing abdominal hysterectomy an infusion of dexmedetomidine was not quite potent enough to provide anaesthesia without additional isoflurane, but the median expired concentration of isoflurane required to maintain haemodynamic variables within predetermined limits was decreased by more than 90%, and required for a shorter period of time.

Ghignone *et al'* reported a 45% reduction in fentanyl requirements in patients undergoing aortocoronary artery bypass surgery after oral clonidine premedication.[45] In a similar study, Flacke and colleagues showed that clonidine premedication reduced sufentanil requirements by 40%.[12] In contrast, Abi-Jaoude *et al* found no opioid sparing effect and no improvement in perioperative haemodynamic stability from clonidine premedication.

There may also be pharmacokinetic reasons for the reduction in opioid requirements. In a study of patients receiving nitrous oxide, isoflurane and an infusion of alfentanil to maintain anaesthesia, premedication with clonidine resulted in a 60% increase in plasma concentration of alfentanil compared with patients who had not received clonidine.

Induction doses of thiopentone are reduced by pretreatment with dexmedetomidine.

Clonidine premedication significantly decreased the requirement for propofol-to maintains anaesthesia during surgery.

Haemodynamic effects during general anaesthesia

Scheinin and colleagues recorded slight decreases in blood pressure and heart rate during surgery, a finding reported in other clinical studies performed to date. The increase in systemic vascular resistance mediated by postsynaptic α_2-adrenoceptors on the peripheral vasculature is blunted by the volatile anaesthetic agents especially halothane.

The bradycardia that occurs with dexmedetomidine and clonidine can be marked (less than 40 beats/min) and is likely be to exacerbate when concomitant drugs also known to produce bradycardia are used. Furst and Weinger examined the cardiovascular and respiratory effects of dexmedetomidine in combination with alfentanil in rats. Dexmedctomidine and alfentanil given independently reduced heart rate. However, in dexmedetomidine-treated rats the addition of alfentanil had no further significant effect on heart rate. Proctor *et al* compared the effects of propofol in dogs, with and without pretreatment with dexmedetomidine (20 $\mu g\ kg^{-1}$). A loading dose of propofol in the dexmedetomidine treated dogs increased heart rate; during subsequent propofol infusions heart rate returned to control levels.[4]

Treatment with anticholinergic agents may attenuate centrally mediated bradycardia produced by the α_2-adrenoceptor agonists, but the α2-adrenoceptor agonists may in turn attenuate the response to anticholinergic agents.

Ventilatory effects during general anaesthesia

Dexmedetomidine (3 μg kg^{-1}) reduced the anaesthetic reguirement (MAC) for isoflurane in dogs from 1.3% to 0.37%. The ventilatory depression caused by this combination of dexmedetomidine and isoflurane was intermediate between the awake state and that during 1.3% (MAC) isoflurane anaesthesia. Although the α_2-adrenoceptor agonists have synergistic analgesic effects with the opioids they do not appear to potentiate respiratory depression. Indeed, combination of the two types of drugs may reduce opioid requirements and so minimize ventilatory side effects. Dexmedetomidine reduces the muscle rigidity induced by opioids.[67]

Conclusion

Alpha2-adrenergic agonists offer a useful and efficient solution to a number of anaesthetic problems and can considerably improve management of some patients. These agents deserve to be more widely used and should be one of the agent types with which every anaesthetist is familiar.

MATERIAL AND METHODS

40 patients undergoing craniotomy for excision of intracranial tumors were studied. Patients were selected based on the following inclusion and exclusion criteria:

Inclusion criteria:

1. patients posted for elective craniotomy for intra cranial space occupying lesion excision
2. ASA grade 1 and 2
3. Age 16 to 65yrs.
4. body weight 40 to 80kg
5. haemoglobin not less than 10gms
6. procedures done in supine,prone or lateral position.

Exclusion criteria:

1. brainstem tumor which cause great swings in hemodynamic parameters
2. patients suffering from cvs,rs or renal disease
3. patients with diabetes mellitus with associated autonomic neuropathy
4. patients who are on drugs that affect BP,heart rate or hormonal response
5. BP in preoperative visit >100mmHg
6. obese patients with body mass index more than 29

7. patients with altered consciousness

Sample size and groups:

The sample size was 40 patients suffering from intacranial tumors

Group 1:was a group of 20 patients premedicated with 3.5micrograms/kg of clonidine orally 90mts prior to induction

Group 2:was a group of 20 patients premedicated with Tab.diazepam 0.2mg/kg body weight orally 90mts before induction.

Pre anaesthetic visit:

An overall assessment of the patient was done as usual.heart rate and blood pressure noted and they were randomly assigned to a group.

Allocation of patients:

Patients were assigned into the two groups by lots taken by a person not taking part in the study and they perscribed the premedicationfor the group. The primary investigator that is the person doing the study, the surgeon and the anaesthetist of the case were anware of the group of the patient.

Premedication:

1.anticonvulsants and steroids which the patients was on is given to the patient

2.group 1 patients are given clonidine in the dose of 3.5micrograms/kg bodyweight, 90mts prior to induction

3.group 2 patients are given diazepam in the dose of 0.2mg/kg bodyweight 90mts prior to induction

In the operating theatre the level of sedation is assessed using ramsay sedation scale.iv infusions are started using 2 16G iv canula in peripheral veins.Radial artery canlationis carried out with 18G iv canula percutaneously either using the transfixationor direct canulation technique after local infilteration.The transducer is fixed at the level of the externalauditory meatus. Baseline heart rate and blood pressure are noted. patient is connected to pulse oximetry and the baseline saturationis noted.

Induction intubation sequence:

IV morphine in a dose of 0.1mg/kg bodyweight is given followed by injection Thiopentone 2.5% solution is given and the induction dose is calculated usingthe pen grip test in which the patient is made to hold a pen in one hand and the dose at which the patient drops the pen is noted. This is followed by injection Pancuronium 0.1mg/kg bodyweight intravenously and IPPV is inatituted with mask and circle system with 33%oxygen and nitrous oxide.inhalational agents Isoflurane is introduced at this stage depending on the heart rate and blood pressure.iv 2%lignocaine 1.5mg/kg is given intravenously 90secs prior to intubation and injection

Thiopentone2.5% is given in a dose of 1mg/kg bodyweight 60secs prior to laryngoscopy and heart rate, systolic, diastolic blood pressure and mean arterial blood pressure are noted before and after laryngoscopy. Heart rate, systolic and diastolic blood pressure and mean arterial pressure are noted before and after every event namely intubation, infiltration with adrenaline, incision, raising the bone flap and extubation and the values are maintained at baseline level to 30%below baseline using other supplemental drugs like metoprolol and propofol infusion and inhalational agents and these drugs are scored using the scoring system shown in the appendix. A urinary catheter is inserted.

Maintenance of anesthesia:

IPPV is instituted with 33%xygen and nitrous oxide to maintain ETCO2 between 25 and 30mmHg.Isoflurane isused to maitainheart rate and blood pressure.Top up doses of pancuronium bromide are given usng a second twitch to TOF stimuli in a peripheral nerve stimulator.At all steps during thesrgery theheart rateand bloodpressure are maintained in the range of baseline to 30%below it using the supplemental drugs and inhalational agents.

Monitoring:

The patient is connected to the following monitors:

ECG

Intra arterial blood pressure

ETCO2

U/O

Blood loss

Neuromuscular monitoring

Pulse oximeter

Fluid therapy:

0.9%NS is given intravenously 2ml/kg bodyweight and then upto 50% of urine output is replaced with NS.Blood loss of lessthan 10% iseither replaced with colloid or crystalloid solutions and a loss morethan 10% is replaced with wholeblood.

Emergence:

Neuromuscular blockadeis reversed with glycopyrolate and neostigmine 40micrograms/kg bodyweight.Patient is extubated and supplemental oxygen is given and patientis shifted to the neuro intensive care unit.The level of sedation is assessed.

Results

The results were interpreted with the ‘t’ test and the ‘p’ value for mean of independent samples were calculated with a confidence interval of 95%.

Table – I shows the sex distribution between the to groups.

Table – II shows the age, weight and duration of anaesthesia between the two groups. There is no significant difference between the two groups.

Table – III shows the sedation scores pre-operatively and postoperatively between the two groups. All the patients [except one in group II] had pre-op and post-op sedation score of 2. there was no significant difference in the sedation score of the two groups.

Table – IV shows the mean HR, SBP, DBP and MAP after each event such as premedication, induction, intubation, infiltration, incision, bone flap and extubation.

1. There was no significant difference in the variables pre-operatively.
2. After premedication there was a significant reduction in SBP, DBP and MAP in the clonidine group compared to diazepam group. There is no significant change in heart rate.
3. After induction there is a significant difference in the difference in SBP, DBP & MAP between the two groups. There is no significant difference in heart rate.
4. After intubation there is a significant difference only in the heart rate between the two

groups. The difference in SBP, DBP & MAP are not significant.

5. After infiltration there is no significant difference in heart rate between the two groups, but there is significant difference in SBP, DBP & MAP between the two groups.
6. After incision there is a significant difference in HR, SBP, DBP & MAP between the two groups.
7. After bone flap there is a significant difference in SBP, DBP & MAP but no significant difference in heart rate between the two groups.
8. After extubation there is no significant difference in HR, SBP, DBP & MAP between the two groups.

Table – V shows the mean of difference in HR, SBP, DBP &MAP before and after various events in surgery like premedication, induction, intubation, infiltration, incision, bone flap and extubation

1. The difference in HR, SBP, DBP & MAP before and after premedication had a significant difference between the two groups.
2. There was no significant difference in HR, SBP, DBP & MAP before and after induction in the two groups.
3. There was a significant difference between the two groups in the variation in DBP & MAP before and after intubation but no significant difference in variation in HR & SBP.
4. There was a significant difference between the two groups in the variation in HR, SBP & MAP before and after infiltration but the variation in DBP was not significant.
5. There was a significant difference between the two groups in the variation in HR, SBP,

DBP & MAP before and after incision.

6. There was no significant difference between the two groups in the variation in HR, SBP, DBP & MAP before and after bone flap.
7. There was a significant difference between the two groups in the variation in HR, SBP & MAP but not DBP before and after extubation.

Table – VI shows the number of patients with the different scores for each agent in the two groups. The score was significantly higher in group II.

DISCUSSION

Premedication is not only for sedation and anxiolysis but also to enhance the quality of induction, maintenance and recovery from anaesthesia.

Primary concern of a neuroanaesthetist in tumor surgery is to avoid fluctuations in blood pressure, coughing and straining. Patients with intracranial tumor are at steep part of intracranial compliance curve so, even small increases in cerebral blood volume cause marked increase in intracranial pressure. Over a wide range changes in cerebral blood flow is directly proportional to $PaCO_2$. Changes in PaO_2 have little influence on cerebral blood flow in the auto regulatory pressure range of 60-130 mm hg. If PaO_2 falls below 60 CBF increases markedly.

Induction and intubation is the most challenging part of neuroanesthesia. Main aim of neuroanesthetist is to obtund the pressor response and tachycardia during intubation. Moreover hypertension has to be prevented even during other events such as infiltration, incision and raising the bone flap. Rise in systolic blood pressure increases the cerebral blood volume there by increasing the intracranial pressure, which in turn leads to decreased cerebral perfusion pressure. Therefore hypertension causes secondary brainstem injury through herniation and ischaemia. Ischaemia in turn leads to enlarging areas of tissue acidosis, which causes cerebral vasomotor paralysis. This causes the cerebral blood flow to become pressure passive.

Herniation occurs at the following sites:

1. Uncal.
2. Transtentorial.
3. Transcalvarial
4. Subfalcine
5. Tonsillar

Uncal herniation causes oculomotor palsy leading on to ptosis, mydriasis, and hemianopia due to posterior cerebral artery compression, hemiparesis due to cerebral peduncle compression. Central tentorial herniation causes decerebrate rigidity due to involvement of corticospinal tract. Midbrain and pontine compression causes irregular respiration. Medullary tonsillar herniation causes hypertension bradycardia and apnea.

Volatile anesthetics impair autoregulation. They increase cerebral blood flow, cerebral blood volume thereby raising ICP. They decrease the cerebral metabolic rate and increase the cerebral blood flow thereby causing an uncoupling of flow and metabolism.

Thiopentone decreases $CMRO_2$ and cerebral blood flow thereby decreasing cerebral neuronal function. It is a cerebral vasoconstrictor. It also attenuates the CO_2 response.

Beta-blockers are used to attenuate the stress response during intubation. They are contraindicated in asthmatics. There are accounts of cardiac arrest in patients with

subarachnoid hemorrhage.

IV lidocaine obtunds laryngosympathetic reflexes, decreases cerebral blood flow and depresses the SA node.

Propofol causes decrease in $CMRO_2$, reduces MAP, but increases the cerebral blood volume. At low doses it is neuroexitatory whereas at high doses it depresses the neuronal function.

Clonidine is an antihypertensive agent used to produce hemodynamic stability during intubation and during the course of surgery. In order to protect the control group (i.e. patients given diazepam) supplemental drugs were used such as beta-blockers, propofol and isoflurane. A scoring system was used to measure the usage of these drugs, which is shown in the appendix. Clonidine also has the unique advantage of producing sedation without causing respiratory depression. It also potentiates morphine-induced analgesia.

As per the study the two groups were similar in the age, sex and weight distribution. The duration of surgery in both the groups ranged from 3 – 4 hours. Patients belonging to both the groups had similar preoperative heart rate and blood pressure.

There was no difference in the preoperative and postoperative sedation scores. All the patients have a sedation score of 2, except one patient in group I who had preoperative sedation score of 1.

There was a significant reduction in the induction dose of thiopentone in the clonidine group. The dose of thiopentone was 14% less in the clonidine group as compared with the diazepam group.

The HR & BP after premedication was significantly lower in the clonidine group. There was a 10 % reduction in heart rate and 8% reduction in MAP in the clonidine group as compared to the 3% reduction in the heart rate and 2% decrease in MAP in the diazepam group.

There was no significant difference in the HR & BP in the two groups during induction and intubation.

During each event in surgery there was a significantly lower HR & BP in the clonidine group (for e.g. there was a 7% difference in the MAP of the two groups after infiltration, 9% after incision and 10% after bone flap). The heart rate in the clonidine group was 8% less than the diazepam group after incision.

When we compare the change in HR & BP during each event in surgery in the two groups there was a better haemodynamic stability in the clonidine group (for e.g. there was a 50% greater change in HR in the diazepam group after infiltration, 60% after incision and 80% more variation after extubation. There was a 50% greater variation in MAP after incision in the diazepam group in comparison with the clonidine group and

90% after infiltration and after extubation).

The blood loss was also lower in the clonidine group but the surgeon's assessment of the field of surgery was not significantly different in the two groups.

There was a 40% reduction in the total score of the clonidine group. The number of patients with higher isoflurane scores was significantly lesser in the clonidine group. 60% had a score of 1. 3% had a score of 2 and none had a score of 3 in the clonidine group. As compared to this, 20% had a score of 1, 75% had a score of 2 and 5% gad a score of 3 in the diazepam group. The usage of propofol infusion was also significantly lower in the clonidine group. 15% had a score of 1, and 5% had a score of 2 and none had a score of 3 in the clonidine group. Whereas in the diazepam group 20% had a sore of 1, 20% had a score of 2 and 5% had a score of 3. the use of metoprolol was also less in the clonidine group. 5% had a score of 2 in the clonidine group whereas 5% had a score of 1 and 10% had a score of 2 in the diazepam group. It is evident from the presented data that the use of supplemental drugs was significantly lower in the clonidine group.

The above data clearly indicates that clonidine offers much greater haemodynamic stability during craniotomy.

Summary

This double blind prospective randomized control study was designed to evaluate the efficacy, usefulness and safety of oral clonidine premedication in neurosurgical patients posted for elective intracranial tumor excision. Oral diazepam in a dose of 0.2 mg/kg served as control.

A total of 40 patients belonging to ASA physical status I & II, belonging to the age group between 16 & 65 years and posted for elective intracranial tumor excision were divided into two groups. 10 males and 10 females in group I received oral clonidine in a dose of 3.5 µg/kg orally 90 minutes prior to induction. 12 males and 8 females in group II received 0.2 mg/kg diazepam prior to induction. The HR, SBP, DBP & MAP were noted during the preoperative visit after premedication and various events such as induction, intubation, infiltration, incision, bone flap and extubation. The use of various supplemental agents such as isoflurane, propofol and Metoprolol were also noted. The following observations were noted:

1. The induction dose of thiopentone was lower in the clonidine group.
2. The HR& BP after premedication were lower in the clonidine group.
3. The HR & BP during various events stated above were lower in the clonidine group except during induction and intubation.
4. The variations in the HR & BP were also less in the clonidine group.
5. Blood loss was lower in the clonidine group.
6. the use of supplemental agents as stated above was also lower in the clonidine group.

Conclusion

We conclude that by using clonidine to manipulate the central MAO pathways involved in sympathetic responses to noxious stimuli can decrease the peaks and valleys (Alpine anaesthesia) and smoothen out anesthesia in craniotomy. A dose of 3.5 µg/kg body weight of clonidine orally 90 minutes prior to induction safely and effectively blocks the pressor and HR response. It also decreases the requirement of other supplemental anaesthetic agents. Clonidine causes dose related sedation, anxiolysis, reduction of secretions, peri operative hemodynamic stability, analgesia, reduction in requirements of anaesthetic agents. Clonidine is beneficial in neurosurgical patients with intracranial tumors for maintenance of hemodynamic stability and avoidance of hyperdynamic episodes, reduction in intracranial pressure and offers protection during cerebral injury. Due to various properties such as controllability, stability of intracranial homeostasis, non interference with neurophysiologic monitoring clonidine can be safely used as a premedicant in neuroanaesthesia.

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